

AMENDMENTS TO THE SPECIFICATION

Please delete the paragraph that begins on page 8, lines 27 and ends on page 9, lines 3, and add the following new paragraphs in its place:

Figure 1 shows the synthesis of the 3'-O-phosphonate and 3'-O-phosphonate, 2'-deoxy-tetrose nucleoside derivatives of naturally-occurring nucleobases starting from (R,S)-2,3-dihydroxy-dihydro-furan-1-one.

Figure 2 shows the synthesis of the 3'-O-phosphonate and 3'-O-phosphonate, 2'-deoxy-tetrose guanosine derivatives starting from (R,R)-2,3-dihydroxy-dihydro-furan-1-one.

Figure 3 shows a first method for the synthesis of the 3'-O-phosphonate and tetrose derivatives substituted on position 2, starting from (R,S)-2,3-dihydroxy-dihydro-furan-1-one.

Figures 4 to 7 each shows an alternative method for the synthesis of the 3'-O-phosphonate tetrose nucleosides derivatives being substituted on position 2.

Figure 8 shows the synthesis of 3'-O-phosphonate tetrose nucleosides derivatives being substituted on position 3, from (R,S)-2,3-dihydroxy-dihydro-furan-1-one.

Figure 9 shows the synthesis of 3'-O-phosphonate tetrose nucleosides derivatives being substituted on position 3, from (S,S)-2,3-dihydroxy-dihydro-furan-1-one.

Each of figures 10 to 12 shows an alternative method for the synthesis of the 3'-O-phosphonate tetrose nucleosides derivatives being substituted on position 2.

Figure 13 shows the synthesis of the 3'-O-phosphonate tetrose nucleosides derivatives being non-substituted on position 2.

Figure 14 shows the synthesis of the 3'-O-phosphonate tetrose adenine nucleosides derivatives being non-substituted on position 2.

Figure 15 schematically shows the synthesis of triphosphate compounds of the present invention.

On page 9, please amend the paragraph starting on line 6 and ending on line 9 to read as follows:

As used herein, and unless stated otherwise, the term "furanose" refers to five-membered cyclic monosaccharides and, by extension, to their sulfur analogues. The numbering of

monosaccharides starts at the carbon next to the oxygen inclosed-enclosed in the ring and is indicated with a prime (').

On page 31, please amend the paragraph starting on line 4 and ending on line 21 to read as follows:

Specific embodiments of bases B suitable for inclusion into the compounds of the present invention include, but are not limited to, hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine-and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine-and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine-and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine-and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine-and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil. Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl.

On page 70, please amend the paragraph starting on line 29 and ending on page 71, line 16, to read as follows:

FIG. 15 illustrates a possible way to synthesize the triphosphate analogue of the ~~of the~~ present invention. Several methods for transforming a nucleoside monophosphate into a triphosphate are known to the person skilled in the art and all these methods are suitable for introducing two phosphate groups onto the phosphonyl group of the phosphonoalkyloxytetrose nucleoside analogs of the present invention. Preferably, a diphosphate is introduced onto the phosphonyl group of the phosphonylated tetrose nucleoside derivatives synthesized following one of the pathways as illustrated by FIGS. 1-14, by first treatment of a solution of the compound

in an organic solvent for example DMF, with dimethylformamide dimethyl acetal at room temperature overnight. After subsequent evaporation of the solvent, the residue is dissolved in an organic solvent again, preferably DMF, and treated with N,N'-carbonyldiimidazole. After 12 h a solution of dibutylammonium pyrophosphate is added and the mixture is kept at room temperature for 2 h. Then the mixture is treated with NH₄OH and subsequently concentrated under reduced pressure. The resulting phosphonyl-diphosphate is purified by methods known to the person skilled in the art, preferably column chromatography, for example reversed phase chromatography.

On page 84, please amend the paragraph heading that starts on line 10 and ends on line 11 to read as follows:

1-(N⁶-benzoyladenin-9-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl-)-L-threofuranose threose (11)

On page 85, please amend the paragraph heading that appears on line 6 to read as follows:

1-(thymin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose (12)

On page 86, please amend the paragraph heading that appears on line 1 to read as follows:

1-(uracil-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose (13)

On page 86, please amend the paragraph heading that starts on line 26 and ends on line 27 to read as follows:

1-(N⁴-acetylcytosin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl-)-L-threofuranose threose (14)

On page 87, please amend the paragraph heading that appears on line 22 to read as follows:

1-(adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose (15)

On page 88, please amend the paragraph heading that appears on line 9 to read as follows:
1-(thymin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose-(16)

On page 88, please amend the paragraph heading that appears on line 25 to read as follows:

1-(uracil-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose-(17)

On page 89, please amend the paragraph heading that appears on line 12 to read as follows:

1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose-(18)

On page 89, please amend the paragraph heading that appears on line 30 to read as follows:

1-(adenin-9-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose-(19)

On page 90, please amend the paragraph heading that appears on line 24 to read as follows:

1-(thymin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose threose-(20)

On page 91, please amend the paragraph heading that appears on line 11 to read as follows:

1-(uracil-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose-(21)

On page 91, please amend the paragraph heading that appears on line 28 to read as follows:

1-(cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threofuranose threose threose-(22)

On page 92, please amend the paragraph heading that appears on line 18 to read as follows:

1-(adenin-9-yl)-3-O-(phosphonomethyl)-L-threofuranose threose sodium salt (3a)

On page 93, please amend the paragraph heading that appears on line 7 to read as follows:
1-(thymin-1-yl)-3-O-(phosphonomethyl)-L-threofuranose threose sodium salt (3b)

On page 93, please amend the paragraph heading that appears on line 21 to read as follows:

1-(uracil-1-yl)-3-O-(phosphonomethyl)-L-threofuranose threose-sodium salt (3c)

On page 94, please amend the paragraph heading that appears on line 7 to read as follows:
1-(cytosin-1-yl)-3-O-(phosphonomethyl)-L-threofuranose threose-sodium salt (3d)

On Page 94, please amend the paragraph heading that appears on line 21 to read as follows:

1-(adenin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threofuranose threose sodium salt (3e)

On page 95, please amend the paragraph heading that appears on line 7 to read as follows:
1-(thymin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threofuranose threose sodium salt (3f)

On page 95, please amend the paragraph heading that appears on line 27 to read as follows:

1-(uracil-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threofuranose threose sodium salt (3g)

On page 96, please amend the paragraph heading that appears on line 14 to read as follows:

1-(cytosin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threofuranose threose-threose sodium salt (3h)

On page 97, please amend the paragraph that begins at line 11 and ends at line 17 to read as follows:

PMDTA (abbreviation for ~~compound 3e~~) shows an IC₅₀ value of 1.0 µg/mL both against HIV-1 and HIV-2. PMDTT (abbreviation for ~~compound 3f~~) has an IC_{sub.50} value of 2.4 µg/mL against HIV-1 and HIV-2. No cytotoxicity was observed for PMDTA nor PMDTT at the highest concentration tested (125 µg/mL), giving the compounds a Si of >125 (PMDTA) and >50 (PMDTT) in these cellular systems. In the cellular test system, both compounds are as active as PMEA and PMPA, and their cytotoxicity is lower.